

Submission under 37 C.F.R. §1.114  
Application No. 10/527,694  
Attorney Docket No. 052203

**REMARKS**

- (1) Claims 4, 6, 7, 11-14 are pending in this application, of which claims 4 and 11-13 have been amended, and claim 14 has been added.
  
- (2) The Applicants filed an amendment on October 14, 2008 in response to the Final Office Action mailed on July 24, 2008. The amendment filed on October 14, 2008 was not entered. Advisory Action mailed on October 30, 2008.
  
- (3) The Applicants herewith file a Request for Continued Examination. The amendment of claims 4 and 11-13, herewith presented, is the same as the previous amendment which was presented on October 14, 2008 but refused to be entered.

Newly added claim 14 is first presented in this Response. Claim 14 recites “wherein the crosslinked high-molecular-weight product includes a moiety derived from the biological low-molecular-weight compound.” As described at page 7 of the original specification, the crosslinked high-molecular-weight product includes a moiety derived from citric acid.
  
- (4) Claims 12 and 13 were rejected under 35 U.S.C. §112, second paragraph. In response, claims 12 and 13 have been amended. Applicants believe that the amendment has overcome the rejection. Reconsideration of the rejection is respectfully requested.

(5) Claims 4, 6, 7 and 11 were rejected under 35 U.S.C. §103(a) as being unpatentable over Nagura et al. (JP 2000-212286) in view of Hermanson (chapter 3, entitled “Zero-Length Cross-Linkers”, PTO-892, Ref U).

The Applicants’ argued in the Response filed on October 14, 2008 that Hermanson does not meet the claimed limitation of “biological low-molecular-weight compound.” In the Advisory Action, the Examiner responds that the Applicants’ argument is not persuasive because the prior art reference must be considered as a whole. The Examiner states that Hermanson teaches the conjugation between two molecules, which can be two protein molecules, a peptide and protein, an oligonucleotide and a protein, or any combination of *small molecules*. The Examiner might consider that the Hermanson’s disclosure of “*small molecules*” corresponds to the claimed “biological low-molecular-weight compound.” However, claim 4 further recite that “the biological low-molecular-weight compound is obtained by modifying at least one carboxyl group of malic acid, oxalacetic acid, citric acid, or *cis*-aconitic acid with N-hydroxysuccinimide or N-hydroxysulfosuccinimide.” Claim 11 has similar limitation. The Hermanson’s disclosure of “*small molecules*” is not specific for one skilled in the art to render obvious the claimed “biological low-molecular-weight compound.” In other words, Hermanson specifically teaches crosslinking without any intervening linker or spacer (that is, by “Zero-Length Cross-Linkers”), but does not teach or suggest at all how to modify Zero-Length Cross-Linkers into others. In

particular, Hermanson does not teach how to crosslink two protein molecules with “small molecules.” Rather, Hermanson teaches that “the presence of these intervening linkers may be detrimental to the intended use.” *See* page 169, the 1st paragraph.

Moreover, Hermanson teaches “Zero-Length Cross-Linkers.” *See* page 169. In case of the zero-length cross linkers taught by Hermanson, no intervening linker or spacer is attached as a result of the crosslinking reaction. The disclosure by Hermanson as to “any combination of *small molecules*” at the last line at page 169 contradicts with the rest of the teachings by Hermanson as a whole. Because Hermanson teaches that “the presence of these intervening linkers may be detrimental to the intended use,” page 169, the 1st paragraph, one skilled in the art does not modify Hermanson such that intervening linkers or small molecules remain in the crosslinked products. It is unpredictable how to modify Hermanson to leave a small molecule in the crosslinked products. It is unpredictable whether the presence of intervening linkers is not detrimental to the intended use.

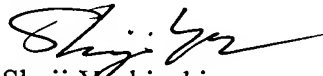
(5) In view of above, the claims are not obvious over the cited references. Applicants submit that that the claims, as herein amended, are in condition for allowance. In particular, the teaching by Hermanson does not leave a moiety derived from the biological low-molecular-weight compound in the crosslinked high-molecular-weight product, as recited in claim 14. The scope of claim 14 excludes the teaching by Hermanson who teaches “Zero-Length Cross-Linkers.”

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(6) Applicants request such action at an early date. If the Examiner believes that this application is not now in condition for allowance, the Examiner is requested to contact Applicants' undersigned representative at the telephone number indicated below to arrange for an interview to expedite the disposition of this case. If this paper is not timely filed, Applicants respectfully petition for an appropriate extension of time. The fees for such an extension or any other fees that may be due with respect to this paper may be charged to Deposit Account No. 50-2866.

Respectfully submitted,

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